REMARKS/ARGUMENTS

Claims 6-12 and 14-23 are active. Claims 13 and 24 have been cancelled without prejudice. The Applicants thank Examiner Ramachandran for indicating in a telephone conversation on May 12, 2008 that the first after-final Amendment had been entered and for agreeing to enter this second after final Amendment for the purpose of reducing and simplifying the issues on appeal. For the convenience of the Examiner, the Applicants' prior arguments and a response to a hypothetical rejection described in the Advisory Action are provided below. Favorable consideration of this amendment and its entry prior to Appeal is respectfully requested.

Rejection—35 U.S.C. §112, second paragraph

Claims 6 and 13 were rejected under 35 U.S.C. 112, first paragraph, for lack of written description for the term "cyclohexylmethyl". This term has been removed from claim 6 and claim 13 has been cancelled thus mooting this rejection.

Neuropathic Pain

The obviousness rejections below are based on an assumption that neuropathic pain is the same as other types of pain or that is identical to allodynia or hyperalgesia. Based on this interpretation, the Examiner alleges that agents which are known to treat other types of pain, such as nociceptive pain characterized by allodynia and hyperalgesia, would also be expected to treat neuropathic pain which may exhibit similar symptoms. This assumption is erroneous for the following reasons.

1. Neuropathic ("neuro-" nerve, "-pathic" to suffer) pain is **NOT** ordinary pain. Unlike normal nociceptive pain which is perceived via normal, healthy neural tissue, neuropathic pain is associated with damage to the neural tissue itself. This abnormal type of

pain is usually perceived as a steady burning and/or "pins and needles" and/or "electric shock" sensations and/or tickling. "With neuropathic pain, the nerve fibers themselves may be damaged, dysfunctional or injured. These damaged nerve fibers send incorrect signals to other pain centers. The impact of nerve fiber injury includes a change in nerve function both at the site of injury and areas around the injury" (previously attached) and at: http://www.medicinenet.com/neuropathic_pain/article.htm

Neuropathic pain is also recognized as a distinct type of pain and has unique characteristics distinguishing it from other types of pain as described by Dorland's Illustrated Medical Dictionary (previously attached) and available at: http://www.mercksource.com/pp/us/cns/cns_hl_dorlands.jspzQzpgzEzzSzppdocszSzuszSzcommonzSzdorlandszSzdorlandzSzdmd_p_02zPzhtm

Moreover, abdominal pain, such as that caused by the Smith, et al. animal model of intestinal allodynia, has characteristics which distinguish it from neuropathic pain (previously attached): http://www.medicinenet.com/abdominal_pain/article.htm.

Furthermore, the cold allodynia of Jorum, et al. which is a type of thermal allodynia associated with neuropathic pain is symptomatically distinguishable from the mechanical or tactile allodynia exemplified by the animal model of Smith, et al., see http://en.wikipedia.org/wiki/Allodynia. For example, the cold allodynia is characterized by pain from normally mild skin temperatures, while mechanical allodynia is abnormal pain in response to light pressure or other tactile stimulation. Thus, different types of nociception characterize thermal and mechanical allodynia.

2. Neuropathic pain is very difficult to treat and is recognized in the art as not being amenable to treatments for normal nociceptive pain. "Unfortunately, neuropathic pain often responds poorly to standard pain treatments and occasionally may get worse instead of better

over time. For some people, it can lead to serious disability",

http://www.medicinenet.com/neuropathic_pain/article.htm.

3. In order to distinguish neuropathic pain from other types of nociceptive pain not associated with nerve damage, the Applicants provide the following definitions from the IASP (International Association for the Study of Pain):

Neuropathic Pain: this term denotes a pain initiated or caused by a primary lesion or dysfunction in the nervous system. Peripheral neuropathic pain occurs when the lesion or dysfunction affects the peripheral nervous system. Central pain may be retained as the term when the lesion or dysfunction affects the central nervous system.

Allodynia: this term denotes a pain due to a stimulus which does not normally provoke pain. The term allodynia was originally introduced to separate from hyperalgesia and hyperesthesia, the conditions seen in patients with lesions of the nervous system where touch, light pressure, or moderate cold or warmth evoke pain when applied to apparently normal skin. Allo means "other' in Greek and is a common prefix for medical conditions that diverge from the expected. Odynia is derived from the Greek word "odune" or "odyne," which is used in "pleurodynia" and "coccydynia" and is similar in meaning to the root from which we derive words with -algia or -algesia in them. Allodynia was suggested following discussions with Professor Paul Potter of the Department of the History of Medicine and Science at The University of Western Ontario.

The words "to normal skin" were used in the original definition but later were omitted in order to remove any suggestion that allodynia applied only to referred pain. Originally, the pain-provoking stimulus was described as 'non-noxious'. However, a stimulus may be noxious at some times and not at others, for example, with intact skin and sunburned skin, and also, the boundaries of noxious stimulation may be hard to delimit. Since the Committee aimed at providing terms for clinical use, it did not wish to define them by reference to the

specific physical characteristics of the stimulation, e.g., pressure in kilopascals per square centimeter. Moreover, even in intact skin there is little evidence one way or the other that a strong painful pinch to a normal person does or does not damage tissue. Accordingly, it was considered to be preferable to define allodynia in terms of the response to clinical stimuli and to point out that the normal response to the stimulus could almost always be tested elsewhere in the body, usually in a corresponding part.

Further, allodynia is taken to apply to conditions which may give rise to sensitization of the skin, e.g. sunburn inflammation, trauma.

It is important to recognize that **allodynia** involves a change in the quality of a sensation, whether tactile, thermal, or of any other sort. The original modality is normally non-painful, but the response is painful. There is thus a loss of specificity of a sensory modality. By contrast, **hyperalgesia** (*q.v.*) represents an augmented response in a specific mode, viz., pain. With other cutaneous modalities, hyperesthesia is the term which corresponds to hyperalgesia, and as with hyperalgesia, the quality is not altered. In allodynia the stimulus mode and the response mode differ, unlike the situation with hyperalgesia. This distinction should not be confused by the fact that allodynia and hyperalgesia can be plotted with overlap along the same continuum of physical intensity in certain circumstances, for example, with pressure or temperature.

Hyperalgesia: this term denotes an increased response to a stimulus which is normally painful. Hyperalgesia reflects increased pain on suprathreshold stimulation. For pain evoked by stimuli that usually are not painful, the term allodynia is preferred, while hyperalgesia is more appropriately used for cases with an increased response at a normal threshold, or at an increased threshold, e.g., in patients with neuropathy. It should also be recognized that with allodynia the stimulus and the response are in different modes, whereas with hyperalgesia they are in the same mode. Current evidence suggests that hyperalgesia is

a consequence of perturbation of the nociceptive system with peripheral or central sensitization, or both, but it is important to distinguish between the clinical phenomena, which this definition emphasizes, and the interpretation, which may well change as knowledge advances.

Rejection—35 U.S.C. §103

Claims 6-12 and 14-17 were rejected under 35 U.S.C. 103(a) as being unpatentable over Gaster et al., EP 0630376[1], in view of Smith et al., Neurosci. Lett. 271:61 and Jorum et al., Pain 101:229. These documents do not render the claimed invention obvious because they do not suggest or provide a reasonable expectation of success for treating neuropathic pain (associated with damaged nerve tissue) using a compound of formula (I). The only reference cited below which refers to neuropathic pain is Jorum, and Jorum does not disclose treating neuropathic pain using a compound of formula I. The teachings of each of the cited references are summarized below:

Invention	Gaster, et al.	Smith, et al.	Jorum
Neuropathic Pain, resulting from "damage to the nervous system", Woolf, et al., Lancet 353:1959.	Pain associated with [0050] irritable bowel syndrome, reflux, dyspepsia, arrhythmia, stroke, anxiety, migraine.	Experimental Intestinal Allodynia: caused by intra-anal insertion of balloon and 5-HT dosing. Inflation of balloon measures distension pressure in intestines as measure of allodynia.	Cold allodynia and hyperalgesia are frequent clinical findings in patients with neuropathic pain.
formula I--Yes	formula I--Yes.	formula I--No	formula I--No
	Compounds of formula I are 5-HT-4 receptor antagonists	5-HT4 receptor antagonist SB 207266	Alfentanil is μ-opioid agonist, not a 5-HT4 receptor antagonist
	No suggestion to treat neuropathic pain.	No suggestion to treat neuropathic pain.	No suggestion that Formula I would treat neuropathic pain.
		Tactile or mechanical allodynia not associated with neuropathic pain.	Thermal allodynia

[1] Cited as EP 0630736 in the Official Action.

None of the cited prior art discloses or suggests using a compound of formula (I) to treat neuropathic pain. Neuropathic pain is a specific type of pain distinct from other types of pain. While the prior art cited by the Examiner discloses compounds of formula (I) for treating **nociceptive** types of pain, there is no suggestion in the prior art that compounds of formula (I) would have any effect at all on **neuropathic pain** associated with damage nerve tissue. Neuropathic pain, as explain in detail above is distinct from nociceptive pain associated with other diseases and denotes a pain initiated or caused by a primary lesion or dysfunction in the nervous system.

Gaster [0050] only describes treatment of irritable bowel syndrome, gastro-oesophagal reflux disease, dyspepsia, atrial arrhythmias and stroke, anxiety and/or migraine with compounds of formula (I) and does not disclose or suggest use of these compounds for treating neuropathic pain.

Smith and Jorum do not disclose the compounds of formula (I) and provide no motivation or suggestion to use compounds of formula (I) and cannot provide a reasonable expectation of success for treating neuropathic pain.

The rejection equates the thermal allodynia of Jorum with the mechanical allodynia of Smith. The Examiner's premise is that since a 5HT4 receptor antagonist (which is not a compound of formula (I) ameliorates intestinal allodynia, that this class of compounds would also ameliorate thermal allodynia of Jorum. Since thermal allodynia is a symptom of neuropathic pain, then if the 5HT receptor antagonist ameliorates allodynia it would also ameliorate neuropathic pain.

The Applicants respectfully traverse this reasoning because:

(i) the prior art does not suggest that neuropathic pain or the thermal allodynia of Jorum can be treated with the class of 5HT-4 receptor antagonists, much less suggest that a compound of formula (I) can treat thermal allodynia. Jorum, in fact, uses a completely

different class of drug—a μ-opioid antagonist. As discussed above, thermal allodynia (Jorum) and mechanical allodynia (Smith) are distinct and involve different types of nociception.

The mechanical of Smith, et al. and thermal allodynia of Jorum involve different types of nociception. Assuming *arguendo* that 5-HT4 receptor antagonists generally treat mechanical allodynia such as the intestinal allodynia in the Smith animal model, there is no reasonable expectation that it would treat thermal allodynia. As discussed above, mechanical and thermal allodynia involve different types of nociception. Smith only describes treatment of intestinal allodynia (**mechanical** or tactile allodynia) and is silent with regard to effects of drugs on thermal allodynia. Moreover, Smith does not suggest treating **neuropathic pain**—a type of pain caused by damage nerve tissue--using a 5-HT4 antagonist.

(ii) Smith does not indicate that the class of 5-HT4 receptor antagonists generally exert anti-allodynic effects, though this is assumed by the argument on page 4 of the Official Action. Smith teaches that "5-HT4 receptor antagonism potentiates inhibition of intestinal allodynia by 5-HT3 receptor antagonism". It does not disclose that a 5-HT4 receptor antagonist would have any effect on intestinal allodynia in the absence of a 5-HT3 receptor antagonist. In fact, page 61, first col. specifically states that "5-HT4 receptor antagonism does **not** affect normal pseudoeffective or visceromotor reflexes evoked by noxious levels of colo-rectal distension in anesthetized or conscious rats (emphasis added)". While the subsequent text on page 61 indicates that "antagonism of this rejection has been shown to reduce nociceptive behaviours" in particular animal models, Smith simply provides no general expectation one way or the other that 5-HT4 receptor antagonism would have any effect on allodynia associated with neuropathic pain, or even on allodynia associated with nociceptive pain. Smith is a general reference that does not suggest treating neuropathic pain characterized by thermal allodynia or even suggest generally treating nociceptive allodynia

using 5-HT4 receptor antagonist. Moreover, Smith does not disclose compounds of formula (I).

Smith does not suggest that 5HT4 receptor antagonists have a direct effect on neuropathic pain or even on nociception associated with experimental intestinal allodynia. Smith only indicates that 5HT4 receptor antagonists **potentiate** inhibition of intestinal allodynia by a **5HT3 receptor antagonist** (see summary, line 3, as well as page 61, right column, line 7 to 9; and Fig. 1 on page 62). Smith merely suggests that "$5HT_4$ receptor activation enhances the ability of $5HT_3$ receptor activation to induce intestinal allodynia" (see summary, last two lines). It is silent about the effects of administering a 5-HT4 antagonist. Thus, the rejection has provided no nexus between the administration of a 5HT4 receptor antagonist *per se* (or specifically a compound of formula I) and treatment of allodynia of any type. Moreover, the Official Action provides no evidence that a compound of formula (I) is **both** an 5-HT3 and 5-HT4 receptor antagonist as taught by Smith. Similarly, there is no evidence of record that mechanical allodynia associated with neuropathic pain is related at all to allodynia in the intestines. Significantly, the test used by Smith does not involve allodynia associated with damaged nerve tissue or any primary lesion or dysfunction in the nervous system. Smith teaches an animal model for a different type of nociceptive pain, not for neuropathic pain. Therefore, the experimental data disclosed by Smith can not be correlated with neuropathic pain in any way. Indeed, in the absence of a primary lesion or dysfunction in the nervous system a pain cannot be defined as neuropathic in nature (see the above definition).

(iii) The Examiner has presumed that structurally distinct compounds that exhibit some degree of antagonism on 5-HT4 receptors as taught by Smith would have similar effects on thermal allodynia associated with neuropathic pain as described by Jorum. However, the Office has not explained why structurally different compounds would have been expected to

exhibit the same effects. The compound of formula I is structurally distinct SB-207266 compound of Smith. Smith provides no evidence that other structurally distinct 5HT4 antagonists like the compound of formula I would have any effect on intestinal allodynia or on thermal allodynia, and no suggestion at all that that a compound of formula (I) would treat neuropathic pain. The Office has demonstrated no nexus between antagonism of 5-HT4 receptors and treatment of neuropathic pain, or even thermal allodynia associated with neuropathic pain.

Moreover, the SB 207266 of Smith does not show any anti-allodynic activity in the test performed by Smith unless it is associated with a 5-HT_3 receptor antagonist. Thus, Smith would be a proper reference only if the present invention was addressed to an association of both a 5-HT_3 and a 5-HT_4 antagonist. Moreover, the test used by Smith. did not involve any primary lesion or dysfunction in the nervous system (nerve damage). Therefore, the experimental data disclosed by Smith cannot be correlated with neuropathic pain in any way. Indeed, in the absence of a primary lesion or dysfunction in the nervous system a pain cannot be defined as neuropathic in nature (see the IASP definition below).

The addition of Jorum does not remedy this deficiency. Jorum discloses that Alfentanil significantly reduced cold allodynia (see summary, line 10). However, this reference is silent about the action of Alfentanil on neuropathic pain. Moreover, Alfentanil is μ-opioid agonist, not a 5-HT_4 receptor antagonist. Thus, Jorum is **non-analogous** art because it discloses a different class of drugs, does not disclose compounds of formula I, and discloses nothing about the effects of drugs on neuropathic pain or thermal allodynia associated with neuropathic pain.

While the Examiner is correct when he states that Jorum teaches that allodynia and hyperalgesia are frequent clinical findings in patient with neuropathic pain, he is wrong when he speculates that inhibiting allodynia in patients would provide a method of treating a

neuropathic pain. Particularly, Jorum is completely silent about the action of Alfentanil on neuoropathic pain. There is no basis at all in Smith to infer that SB 207266 shows an anti-allodynic activity in the absence of a 5-HT_3 receptor antagonist, and no basis in Jorum to infer that inhibiting allodynia in patients would provide a method of treating a neuropathic pain.

On the other hand, the inventors show in Figs. 1 and 2, the efficacy of the compound of formula (I) to treat neuropathic pain in two different models: pain threshold after sciatic nerve ligature and by the effects on pain threshold in diabetic neuropathy. As shown, control animals that did not receive the compound of formula (I) have significantly lower pain thresholds than treated animals and a dose-response relationship was demonstrated.

Therefore, since the prior art does not disclose, suggest or provide a reasonable expectation of success for the invention, the Applicants respectfully request that this rejection be withdrawn.

Rejection—35 U.S.C. §103

Claims 6-12 and 14-17 were rejected under 35 U.S.C. 103(a) as being unpatentable over Gaster et al., EP 0630736, in further in view of Burnstein et al., Brain 123:1703 and Jorum et al., Pain 101:229. Gaster and Jorum have been addressed above. Neither discloses or suggests using a compound of formula (I) to treat neuropathic pain. Only Gaster even describes a compound of formula (I) and Jorum is directed to treatments using a different class of drugs: μ-opioid agonists, not 5-HT_4 receptor antagonists.

Burnstein describe the development of cutaneous allodynia during a migraine attack. However, nothing in this reference teaches or suggests that a class of drugs capable of treating cutaneous allodynia will successfully treat migraine, or more importantly, neuropathic pain.

Significantly, there is no link whatsoever between migraine (which is thought to arise from chemical activation of sensory nerves that supply intracranial blood vessels and meninges, see the first six lines of Burnstein) and neuropathic pain which, in contrast, is caused by a primary lesion or dysfunction in the nervous system. Thus, there cannot be any reasonable expectation of success for treating neuropathic pain using a compound that treats cutaneous allodynia or even migraine.

Moreover, to link migraine to neuropathic pain via allodynia, Burstein should teach that a fully developed migraine attack benefits from a possible drug capable of treating cutaneous allodynia. In contrast, Bernstein is completely silent about the effects on migraine of drugs capable of treating cutaneous allodynia.

In turn, Jorum does not establish a link between the treatment of allodynia and the treatment of neuropathic pain. Indeed, Jorum et al. teaches that Alfentanil is useful to treat allodynia only. However, it is completely silent about the action of Alfentanil on the neuoropathic pain. Thus, there is no suggestion or reasonable expectation of success in Gaster, Burstein or Jorum that inhibiting allodynia would provide a method of treating a neuropathic pain. Accordingly, the Applicants respectfully request that this rejection be withdrawn as none of the cited prior art suggests or provide a reasonable expectation of success for use of a compound of formula I to treat neuropathic pain.

Rejection—35 U.S.C. §103

Claims 18-20 were rejected under 35 U.S.C. 103(a) as being unpatentable over Gaster et al., EP 0630376[2], in view of Smith et al., Neurosci. Lett. 271:61 and Jorum et al., Pain 101:229, and further in view of Wickenden, U.S. Patent No. 6,326,385. The primary references have been addressed above--none suggest using a compound of formula (I) to treat

[2] Cited as EP 0630736 in the Official Action.

neuropathic pain. Wickenden is cited as showing the neuropathic pain is associated with injury to the central or peripheral nervous system. The argument is also based on the assumption that 5-HT4 receptor antagonist will treat allodynia associated with any disease including thermal allodynia described by Jorum. There is no suggestion of support for this assumption the prior art. Since the prior art does not disclose that the class of 5HT4 receptor antagonists are generally useful for treating neuropathic pain, or, specifically, that a compound of formula (I) should be used for this purpose, this rejection should also be withdrawn.

Rejection—35 U.S.C. §103

Claims 20-23 were rejected under 35 U.S.C. 103(a) as being unpatentable over Gaster et al., EP 0630376[3], in view of Smith et al., Neurosci. Lett. 271:61 and Jorum et al., Pain 101:229, and further in view of Omoigui, et al., U.S. 2004/0038874. The primary references have been addressed above--none suggest using a compound of formula (I) to treat neuropathic pain. Omoigui was cited as showing that neuropathic pain is associated with inflammation. This document describes "treating persistent pain disorders by inhibiting the biochemical mediators of **inflammation** (emphasis added)", abstract. Paragraph [0051] refers to release of Substance P from injured nerves as an "important early event in the induction of neuropathic pain". However, these teachings are merely hypothetical and theoretical as clear from paragraph [0001]:

> The invention relates to a method of treatment of persistent pain by application of Sota Omoigui's Law, which states: The origin of all pain is inflammation and the inflammatory response. Irrespective of the type of pain whether it is acute pain as in a sprain, sports injury of Euro charge jellyfish sting or whether it is chronic pain as in arthritis, migraine pain, back or neck pain from herniated disks, REDCAPS pain, migraine, Fibromyalgia, Interstitial cystitis, Neuropathic pain, Post-stroke pain, etc., the underlying basis the inflammation and the inflammatory response.

[3] Cited as EP 0630736 in the Official Action.

> Irrespective of the characteristic of the pain, whether it is sharp, dull, aching, burning, stabbing, numbing or tingling, all pain arise from inflammation and the inflammatory process.

According to the author, the origin of all kinds of pain are the biochemical mediators of inflammation and the inflammatory response, so that, to treat pain, it is sufficient to block these mediators and block the signals they send up through the nerve cells. Unfortunately, most of this patent publication is based on a literature reference published on "medical hypothesis", a journal of the Elsevier group which has the purpose "to publish interesting theoretical papers" and to "consider radical, speculative and non-mainstream scientific ideas", see Enclosure 1. The reference is "The biochemical origin of pain--Proposing a new law of pain: The origin of all pain is inflammation and the inflammatory response. Part 1 of 2--A unifying law of pain", Medical Hypotheses, Vo. 69(1), pages-82 (see Enclosure 2).

The rest of Omoigui's patent publication is based on a literature reference E-published on August 27, 2007 in the very same journal "The biochemical origin of pain: The origin of all pain is inflammation and the inflammatory response. Part 2 of 3--Inflammatory profile of pain syndromes, see Enclosure 3. Accordingly, the content of such literature references is highly speculative and theoretical--it lacks confirmatory scientific support in the scientific and academic world.

Moreover, a plain reading of Omoigui [0051] and [0068-0069] does not reveal a common mechanism linked to Substance P between the naturopathic pain and pain associated with migraine. Paragraph [0051] simply states that the induction of neuropathic pain is a chain of events which comprises the release of substance P from injured nerves which then increases local Tumor Necrosis Factor α (TNF-α) production, which then together attract and activate immune monocytes and macrophages. The mechanism is then much more complex than that considered by the Examiner, and involves another product (TNF-α) and the activation of specific cellular types.

Paragraph [0051] ends stating that inhibition of macrophage recruitment to the nerve injury site, or pharmacological interference with TNF-α production has been shown to reduce both the neuropathological and behavioral manifestations of neuropathic pain states. There is no mention of treatment of neuropathic pain states with any substance interfering with Substance P.

Paragraphs [0068-0069] deal with a completely different theoretical mechanism. Here, and in particular in the last 4 lines of page 7 and in the last 18 lines of page 8, substance P is only associated with calcitonin gene-related peptides (CGRP) and it is said that this latter molecule is responsive for vasodilatation (a well known cause of migraine) and an increase in dural arterial flow, but not substance P. Substance P is said to have a role in mediating plasma leakage from small veins in the *dura mater* (which is not known to be related to migraine).

Even if both these sections of Omoigui deal with Substance P, the mechanisms involved are substantially different and involve different tissues, different biochemical products, and different cellular types. It cannot simply be concluded that treating with a substance interfering with substance P would result in a treatment of both neuropathic pain and migraine. There is no reasonable expectation of such in Omoigui.

On the contrary, the scientific literature shows that receptor antagonists for substance P are not effective for analgesia, see Hill, TIBS 21, "NK1 (substance P) receptor antagonist--why are they not analgesic in humans?", see Enclosure 4. Accordingly, the teachings of Omoigui are theoretical and cannot provide any reasonable expectation of success for the invention. As discussed above, these teachings are hypothetical and not supported by the scientific literature. Accordingly, this rejection may now be withdrawn.

Hypothetical Rejection based on Kayser, et al.

The Advisory Action indicates that the Examiner might impose an obviousness rejection based on Kayser, et al., Brit. J. Pharm. 137:1287. The Applicants reiterate their remarks above with respect to the other three cited references Gaster, et al., Burnstein, et al. and Jorum, et al. The Applicants respectfully submit that this rejection should not be imposed based on the differences between the invention and the cited documents. Moreover, with respect to the teachings of Kayser, et al., the Applicants note that there is no link between migraine and neuropathic pain and that hyperaclgesia and allodynia are generic clinical findings of several kinds of pain and are not peculiar of neuropathic pain. The Applicants also take issue with the Examiner's assertion that antimigraine 5-HT 1B/1D serotonin receptor agonist exerted anti-allodynic effects in the rat model of trigeminal neuropathic pain. Obviously, the 5-HT 1B/1D receptors of Kayser are different from the 5-HT4 receptors of Gaster, et al. and the Examiner provides no motivation to substitute one for the other. Moreover, Gaster is cited as indicating that the compounds of the invention are 5-HT antagonists, while Kayser is cited as teaching compounds that are 5-HT 1B/1D receptor agonists. In view of the known opposite effects of agonists and antagonists, the Examiner has not explained why one would substitute one for the other. Therefore, the Applicants respectfully submit that there is no *prima facie* basis for imposing this hypothetical rejection.

Conclusion

In view of the amendments and remarks above, the Applicants respectfully submit that this application is now in condition for allowance. Early notice of such is earnestly requested.

Respectfully submitted,

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